

5      **WHAT IS CLAIMED IS:**

10      1.      A method of treating or reducing the risk of acquiring osteoporosis comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

15      2.      A method of treating or reducing the risk of acquiring hypercholesterolemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

25      3.      A method of treating or reducing the risk of acquiring hyperlipidemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

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4. A method of treating or reducing the risk of acquiring atherosclerosis comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

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5. A method of treating or reducing the risk of acquiring breast cancer comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

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6. A method of treating or reducing the risk of acquiring endometrial cancer comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

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5           7.     A method of treating or reducing the risk of acquiring  
uterine cancer comprising increasing levels of a sex steroid precursor  
selected from the group consisting of dehydroepiandrosterone,  
dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a  
patient in need of said treatment or said reduction, and further  
10 comprising administering to said patient a therapeutically effective  
amount of a selective estrogen receptor modulator as part of a  
combination therapy.

15           8.     A method of treating or reducing the risk of acquiring  
ovarian cancer comprising increasing levels of a sex steroid precursor  
selected from the group consisting of dehydroepiandrosterone,  
dehydroepiandrosterone-sulfate and androst-5-ene-3 $\beta$ ,17 $\beta$ -diol , in a  
patient in need of said treatment or said reduction, and further  
comprising administering to said patient a therapeutically effective  
20 amount of a selective estrogen receptor modulator as part of a  
combination therapy.

25           9.     The method of claim 1 further comprising the step of  
administering a therapeutically effective amount of a bisphosphonate as  
part of said combination therapy.

30           10.    A kit comprising a first container containing a  
therapeutically effective amount of at least one sex steroid precursor  
selected from the group consisting of dehydroepiandrosterone,  
dehydroepiandrosterone-sulfate, androst-5-ene-3 $\beta$ ,17 $\beta$ -diol and any  
prodrug that is converted in vivo any into the foregoing precursors; and

5 further comprising a second container containing a therapeutically effective amount of at least one selective estrogen receptor modulator .

11. A pharmaceutical composition comprising:

a) a pharmaceutically acceptable excipient, diluent or carrier;

10 b) a therapeutically effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 $\beta$ ,17 $\beta$ -diol and a prodrug that is converted *in vivo* into any of the foregoing sex steroid precursors; and

15 c) a therapeutically effective amount of at least one selective estrogen receptor modulator .

20 12. A kit of claim 10 comprising at least one additional container of said kit that contains a therapeutically effective amount of at least one bisphosphonate.

25 13. A pharmaceutical composition of claim 11 wherein said composition further comprising a therapeutically effective amount of at least one bisphosphonate.

14. The method of claim 1 further comprising administering a therapeutically effective amount of a progestin.

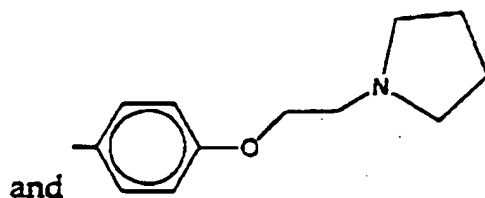
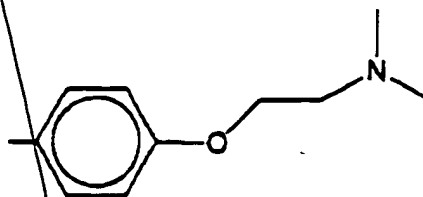
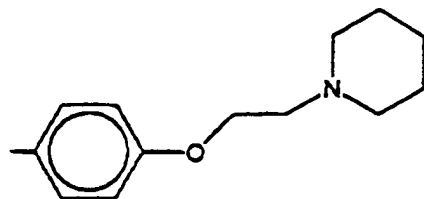
30 15. The method of Claim 1 wherein the selective estrogen receptor modulator has a molecular formula with the following features :

a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or

5 substituted by a hydroxyl group or a group converted *in vivo* to hydroxyl;

b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof.

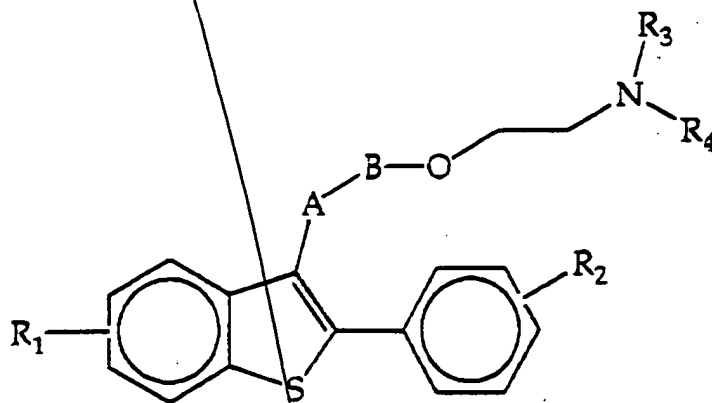
10 16. A method of Claims 15 wherein the side chain is selected from the group consisting of :



15 17. The method of Claim 15 wherein the two aromatic rings are both phenyl and wherein the side chain possesses a moiety selected from the group consisting of a methine, a methylene, -CO, -O-, and -S-, an aromatic ring, and a tertiary amine function or salt thereof

20 18. The method of Claim 15 wherein the selective estrogen receptor modulator is selected from the group consisting of a benzothiophene derivative, triphenylethylene derivative, indole derivative, benzopyran derivative, and centchroman derivative.

5            19. The method of Claim 15 wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:



10            wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl ;

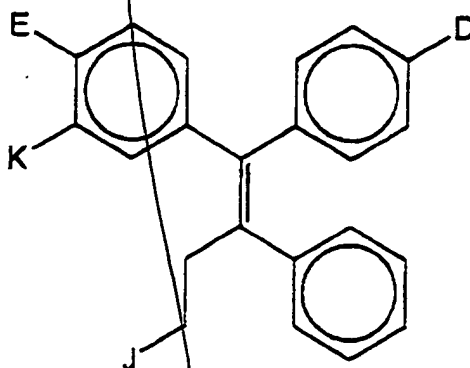
             wherein R<sub>3</sub> and R<sub>4</sub> are either independently selected from the group consisting of : C1-C4 alkyl, or wherein R<sub>3</sub>, R<sub>4</sub> and the nitrogen to which they are bound, together are any structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;

             wherein A is selected from the group consisting of -CO-, -CHOH, and -CH<sub>2</sub>-;

20            wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC<sub>4</sub>H<sub>2</sub>N<sub>2</sub>-.

25            20. The method of Claim 19 wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

5            21. The method of Claim 15 wherein the selective estrogen receptor modulator is a triphenylethylene derivative compound of the following formula :



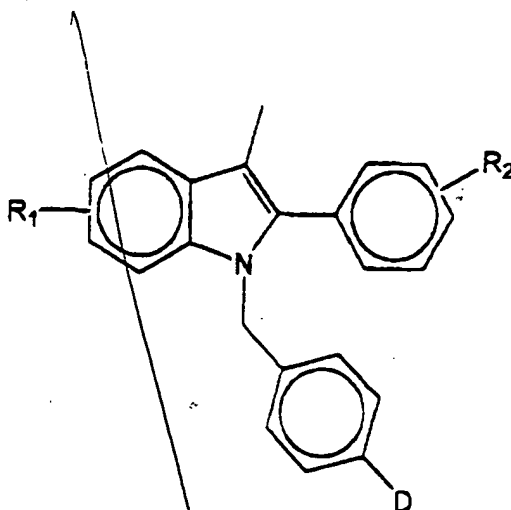
10            wherein D is  $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$  or  $-\text{CH}=\text{CH}-\text{COOH}$  ( $\text{R}_3$  and  $\text{R}_4$  either being independently selected from the group consisting of C1-C4 alkyl, or  $\text{R}_3$ ,  $\text{R}_4$ , and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-  
15            pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

             wherein E and K are independently hydrogen or hydroxyl;

             wherein J is hydrogen or halogen.

20            22. The method of claim 12 wherein selective estrogen receptor modulator is Tamoxifen, OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, and GW5638.

25            23. The method of Claim 15 wherein the selective estrogen receptor modulator is an indole derivative compound of the following formula:

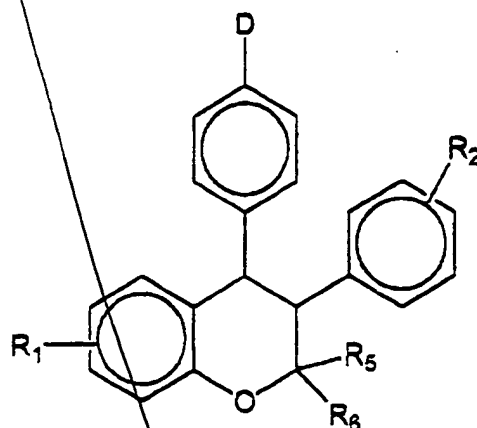


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10 wherein  $D$  is  $-OCH_2CH_2N(R_3)R_4$  ( $R_3$  and  $R_4$  either being independently selected from the group consisting of  $C_1$ - $C_4$  alkyl, or  $R_3$ ,  $R_4$  and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

15 wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

24. The method of Claim 15 wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula :





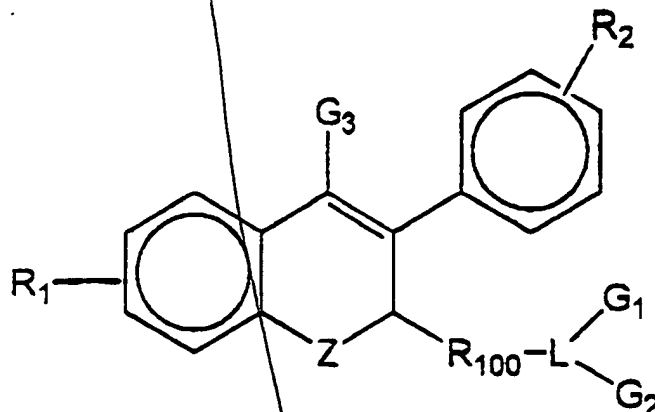
wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of: hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;

wherein  $R_5$  and  $R_6$  are independently hydrogen or  $C_1$ - $C_6$  alkyl;

wherein D is  $-OCH_2CH_2N(R_3)R_4$  ( $R_3$  and  $R_4$  either being independently selected from the group consisting of  $C_1$ - $C_4$  alkyl, or  $R_3$ ,  $R_4$  and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

25. The method of Claim 24 wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-7-methoxychroman).

26. The method of Claim 15 wherein the selective estrogen receptor modulator has the following formula :



wherein  $R_1$  and  $R_2$  are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo ;

wherein  $Z$  is a bivalent closing moiety ;

wherein the  $R_{100}$  is a bivalent moiety which distances  $L$  from the B-ring by 4-10 intervening atoms ;

wherein  $L$  is a bivalent or trivalent polar moiety selected from the group of  $-SO-$ ,  $-CON-$ ,  $-N<$ , and  $-SON<$  ;

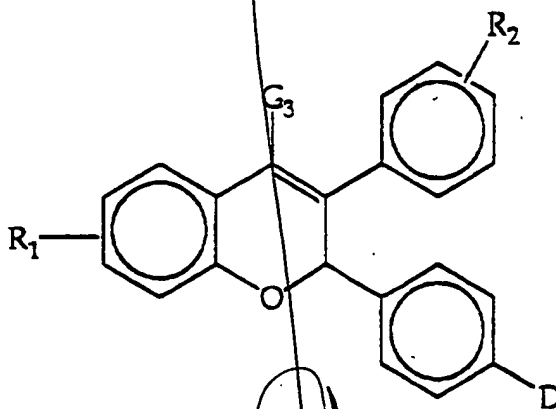
wherein  $G_1$  is selected from the group consisting of hydrogen, a  $C_1$  to  $C_5$  hydrocarbon or a bivalent moiety which joins  $G_2$  and  $L$  to form a 5- to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein  $G_2$  is either absent or selected from the group consisting of hydrogen, a  $C_1$  to  $C_5$  hydrocarbon or a bivalent moiety which joins  $G_1$  and  $L$  to form a 5- to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein  $G_3$  is selected from the group consisting of hydrogen, methyl and ethyl.

5            27. The method of Claim 26, wherein Z is selected from the group consisting of -O-, -NH-, -S-, and -CH<sub>2</sub>-.

28. The method of Claim 27, wherein the compound is a benzopyran derivative of the following general structure :

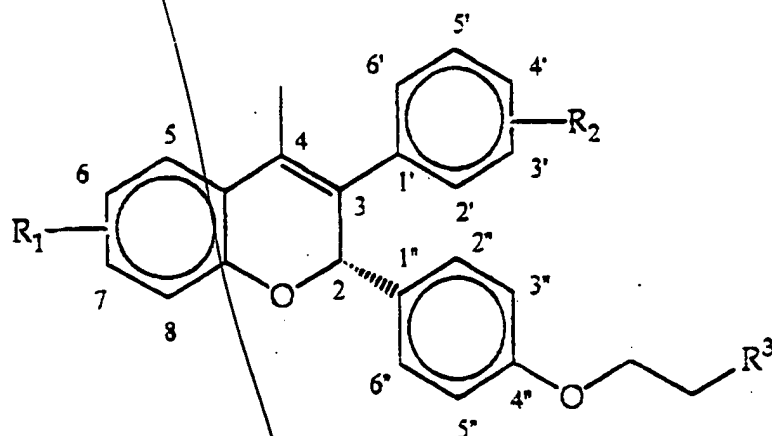


10            wherein D is -OCH<sub>2</sub>CH<sub>2</sub>N(R<sub>3</sub>)R<sub>4</sub> (R<sub>3</sub> and R<sub>4</sub> either being independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, or R<sub>3</sub>, R<sub>4</sub> and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

15            wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of: hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

20            29. The method of Claim 28, wherein the benzopyran derivative is an optically active compound having an absolute configuration S on carbon 2 or pharmaceutically acceptable salt thereof, said compound having the molecular structure:

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wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of hydroxyl and a moiety convertible *in vivo* to hydroxyl;

wherein  $R^3$  is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and  $NRaRb$  ( $Ra$  and  $Rb$  being independently hydrogen, straight or branched  $C_1-C_6$  alkyl, straight or branched  $C_2-C_6$  alkenyl, and straight or branched  $C_2-C_6$  alkynyl).

30. The method of claim 29 wherein said compound or salt substantially lacks (2R)-enantiomer.

31. The method of claim 28 where said selective estrogen receptor modulator is selected from the group consisting of:

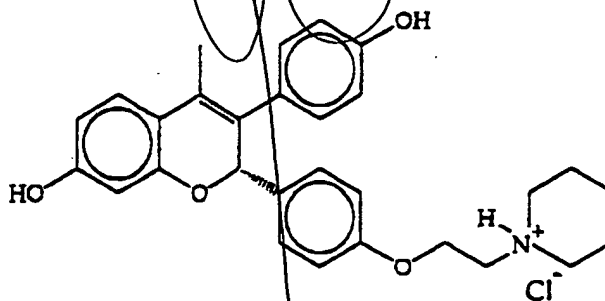
CC(C)(C)OC(=O)c1ccc(cc1)/C=C2/C(=C/C(=C/C(=C2)OC(=O)c3ccc(cc3)OCCCN4CCCCC4)OC(=O)c5ccc(cc5)C(C)(C)C)/CCCOC(=O)c1ccc(cc1)C2=C(C(=O)c3ccc(cc3)OCCN4CCCCC4)C(=C5C=C(C)C=C(C5)OC)O2CCOC(=O)c1ccc2c(c1)oc([C@H](c3ccccc3OCCCN4CCCCC4)c5ccccc5C(=O)OCC)cc2CCOC(=O)c1ccc2c(c1)oc3c2c(c4ccccc4OCCN4CCCCC4)cc5ccccc53

5           32.    The method of claim 29 wherein the benzopyran derivative  
is a salt of an acid selected from the group consisting of acetic acid, adipic  
acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric  
acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid,  
hydrochlorothiazide acid, hydroxy-naphthoic acid, lactic acid, maleic  
10   acid,   methanesulfonic   acid,   methylsulfuric   acid,   1,5-  
naphthalenedisulfonic acid, nitric acid, palmitic acid, pivalic acid,  
phosphoric acid, propionic acid, succinic acid, sulfuric acid, tartaric acid,  
terephthalic acid, p-toluenesulfonic acid, and valeric acid.

15           33.    The method of claim 32 wherein the acid is hydrochloric  
acid.

          34.    The method of claim 1 wherein said selective estrogen  
receptor modulator is:

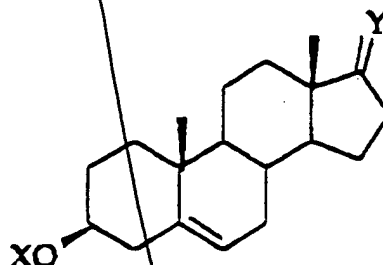
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20           and an amount of a sex steroid precursor selected from the group  
consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate,  
androst-5-ene-3 $\beta$ ,17 $\beta$ -diol.

25           35.    The method of claim 1 wherein the sex steroid precursor is  
dehydroepiandrosterone.

5                    36.    The method of claim 1 wherein the compound converted *in vivo* to into sex steroid precursor has the general formula :



10                    wherein X is selected from the group consisting of H- , ROC-,  
RCO<sub>2</sub>CHRa- and RbSO<sub>2</sub>- (R being selected from the group consisting of  
hydrogen, straight- or branched-(C<sub>1</sub>-C<sub>18</sub>) alkyl, straight- or branched-(C<sub>2</sub>-  
C<sub>18</sub>) alkenyl, straight- or branched-(C<sub>2</sub>-C<sub>18</sub>) alkynyl, aryl, furyl, straight-  
or branched-(C<sub>1</sub>-C<sub>18</sub>) alkoxy, straight- or branched-(C<sub>2</sub>-C<sub>18</sub>) alkenyloxy,  
15                    straight- or branched-(C<sub>2</sub>-C<sub>18</sub>) alkynyloxy, aryloxy, furyloxy, and  
halogeno or carboxyl analogs of the foregoing; Ra being hydrogen or  
(C<sub>1</sub>-C<sub>6</sub>) alkyl; and, Rb being selected from the group consisting of  
hydroxyl (or salts thereof), methyl, phenyl and p-toluyyl);

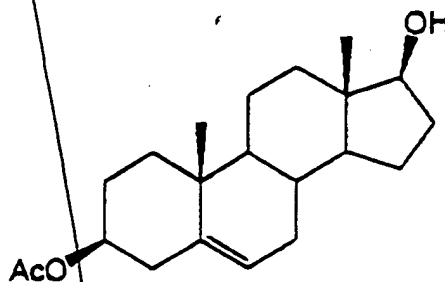
20                    wherein Y is carbonyl oxygen or Y represent a β-OX (X having the  
same meaning as above) and α-H.

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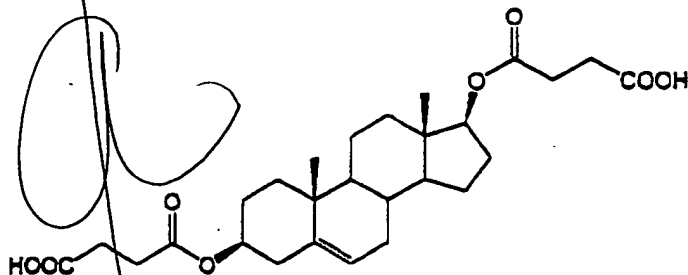
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37. The method of claim 1 wherein the compound converted *in vivo* to into sex steroid precursor is selected from the group consisting of :

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38. The method of claim 1, further comprising administering a therapeutically effective amount of a progestin.

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